



# **Development, QA/QC and Status of Study Protocols**

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**Perchlorate Stakeholders Forum**

**Sponsored by the IPSC**

**Henderson, NV**

**19-21 May 1998**



# Outline

- **Development of Study Protocols**
- **QA/QC Procedures**
- **Status of Studies**



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## **May 1997 Perchlorate Study Protocol Review Meeting**

- **Expert Peer Review Panel:**
  - **Bring together the experts to determine what toxicology studies need to be conducted**
  - **Discuss protocols for 90-day and developmental neurotoxicity studies**
  - **Discuss additional studies needed**
  - **Prioritize all studies without regard to funding**



## **May 1997 Perchlorate Study Protocol Review Meeting**

- **Dr. Joe Brown, California EPA, Office of Environmental Health Hazard Assessment**
- **Dr. Dan Caldwell, Toxicologist, Belle Meade, NJ**
- **Dr. Dorothy Canter, U.S. EPA, Office of Solid Waste and Emergency Response**
- **Dr. Charles Capen, Ohio State University, Department of Veterinary Biomedicine**
- **Dr. John Christopher, California EPA, Department of Toxic Substances Control**
- **Dr. Marvin Friedman, Cytec Industries, Inc.**



## **May 1997 Perchlorate Study Protocol Review Meeting**

- **Mr. Greg Harvey, U.S. Air Force, Wright-Patterson Air Force Base**
- **Ms. Annie Jarabek, U.S. EPA, National Center for Environmental Assessment**
- **Dr. David Morry, California EPA, Office of Environmental Health Hazard Assessment**
- **Dr. Marilyn Underwood, California Department of Health Services**
- **Dr. David R. Mattie, AFRL, USAF**



## **May 1997 Perchlorate Study Protocol Review Meeting Outcomes**

- **Prioritized list of 8 studies**
- **Agreement to continue as reviewers to develop and refine study protocols**
- **All final protocol information to be made available to the public through use of the world-wide-web on TERA's site**
- **Add reviewers and experts as needed**



## **TOXICITY STUDIES**

### **Recommended List:**

- **1. 90-Day Subchronic Study**
- **2. Developmental neurotoxicity Study**
- **3. Genotoxicity assays**
- **4. Mechanistic**
- **5. ADME - Absorption, Distribution, Metabolism and Elimination**
- **6. Developmental Study**
- **7. 2-Generation Reproductive Study**
- **8. Immunotoxicity**



## **Protocol Review Team (as of 12 Jan 98)**

- **Dr. Joe Brown, California EPA, Office of Environmental Health Hazard Assessment (OEHHA)**
- **Dr. Dan Caldwell, Toxicologist, Belle Meade, NJ**
- **Dr. Dorthy Canter, US EPA (OSWER)**
- **Dr. Charles Capen, Ohio State University**
- **Dr. John Christopher, California EPA, DTSC**
- **Dr. Eric Clegg, US EPA (NCEA)**
- **Dr. Kevin Crofton, US EPA National Health and Environmental Effects Research Laboratory (NHEERL)**
- **Dr. Vicki Dellarco, US EPA (OW)**



## **Protocol Review Team (as of 12 Jan 98)**

- **Dr. Marvin Friedman, Cytec Industries, Inc**
- **Mr. Greg Harvey, USAF, Wright Patterson AFB**
- **Ms. Annie Jarabek, US EPA (NCEA)**
- **Mr. Kevin Mayer, US EPA (Region IX)**
- **Dr. David Morry, California EPA (OEHHA)**
- **MaryJane Selgrade, US EPA (NHEERL)**
- **Dr. Marilyn Underwood, California Department of Health Services**
- **Ms. Brenda Pohlmann, Nevada Division of Environmental Protection**



## Status of Study Protocols

- **6 out of 8 are in progress**
- **Mechanistic and kinetic protocols are still being developed**



## Outline

- **Development of Study Protocols**
- QA/QC Procedures
- **Status of Studies**



## **QA/QC Procedures Air Force Sponsored Studies**

- **Contract lab delivers draft report to AFRL for review by contract monitor and project director**
- **Review includes:**
  - **QA/QC to confirm study conducted according to protocol requirements**
  - **Contractual review for form and contract requirements**



## **QA/QC Procedures Air Force Sponsored Studies**

- **Comments returned to contract lab**
  - **Editorial, contractual, format**
- **Contract lab addresses comments**
- **Final draft to AFRL for technical review by Senior Scientist and associates with necessary expertise**
- **Contractor addresses final comments**



# **QA/QC Procedures**

## **Air Force Sponsored Studies**

- **Final report delivered to AFRL**
- **Final report delivered to EPA/NCEA within 48 hours**
- **Total review time: 45 days**



## **QA/QC Procedures PSG Sponsored Studies**

- **Contract lab delivers draft report to TERA/PSG for review by contract monitor**
- **Review includes:**
  - **QA/QC to confirm study conducted according to protocol requirements**
  - **Contractual review for form and contract requirements**
  - **Editorial, contractual, format**



## **QA/QC Procedures PSG Sponsored Studies**

- **Draft report undergoes technical review by AFRL**
- **Contractor addresses all comments**
- **Final report delivered to TERA/PSG**
- **Final report delivered to EPA/NCEA within 48 hours**
- **Total review time: 32 days**



# QA/QC Procedures Summary

- **Standardized review process for all studies**
- **Technical review by AF Senior Scientist team**
- **Commitment to expedited review process to accommodate assessment schedule**



## Outline

- **Development of Study Protocols**
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## **TOXICITY STUDIES**

### **Recommended List:**

- **1. 90-Day Subchronic Study**
- **2. Developmental neurotoxicity Study**
- **3. Genotoxicity assays**
- **4. Mechanistic**
- **5. ADME - Absorption, Distribution, Metabolism and Elimination**
- **6. Developmental Study**
- **7. 2-Generation Reproductive Study**
- **8. Immunotoxicity**



## **1. 90-day subchronic study**

- **Guideline study: OPPTS 870.3100**
- **Added additional tests for:**
  - **Reproductive parameters**
  - **Mutagenic effects in bone marrow**
  - **Thyroid hormone levels**
- **Contract lab with necessary expertise**
- **Air Force collaboration**
  - **Stability study and dose verification**
  - **Hormone analysis**



## **2. Developmental Neurotoxicity Study**

- **Guideline study: OPPTS 870.6300**
  - **Added thyroid histopathology of pups at day five**
- **Contract lab with demonstrated proficiency in this specialized study**
- **Air Force collaboration**
  - **Stability study and dose verification**
  - **Thyroid histopathology**
  - **Hormone analysis**



### 3. Genotoxicity Assays

- **Tests:**
  - **Ames Bacterial Mutation Assay (40 CFR 798.5265)**
  - **Mouse Lymphoma Assay (40 CFR 798.5300)**
  - **In vivo mouse bone marrow micronucleus test (40 CFR 798.5395)**
- **Contract lab with necessary expertise**



## 4. Mechanistic

- **Literature search for perchlorate discharge test by AFRL**
- **Studies proposed:**
  - **Effects of perchlorate in the developing animal**
  - **Iodine uptake**
  - **Biomarkers of Perchlorate Neurotoxicity**
- **By Neurotoxicity Division of USEPA NHEERL**



## **5. ADME - Absorption, Distribution, Metabolism and Elimination**

- **Study protocols under development**
  - **Perchorate kinetics**
  - **Iodine inhibition kinetics**
- **By Air Force toxicology lab**



## 6. Developmental Study

- **Guideline study: OPPTS 870.3700**
- **Additional groups added to study**
- **Added hormone analysis and thyroid histopathology**
- **Contract lab with expertise**



## **7. 2-Generation Reproductive Study**

- **Guideline study: OPPTS 870.3800**
- **Added analysis of thyroid hormones and histopathology of thyroids at additional timepoints**
- **Contract lab with necessary expertise**



## 8. Immunotoxicity

- Incorporated aspects of guideline study (OPPTS 870.7800) to address concerns for perchlorate
- Proposed by Air Force Post Doc
- At Medical University of South Carolina
- Air Force collaboration



## **TOXICITY STUDIES**

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## Report Status

- **Final and interim reports will be sent to NCEA/EPA for assessment and the setting of the revised RfD**



## Report Status

- **Final Reports available for EPA assessment:**
  - **1. 90-Day (Spring 98)**
  - **2. Developmental neurotoxicity study (Spring 98)**
  - **3. Genotoxicity assays (Summer 98)**
  - **6. Developmental study (Summer 98)**



## Report Status

- **Interim reports available for EPA assessment:**
  - **5. ADME - Absorption, Distribution, Metabolism and Elimination (Summer 98)**
  - **7. 2 Generation reproductive (Summer 98)**
  - **8. Immunotoxicity (Summer 98)**



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